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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,570	BOEHM ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *11-14,25-36 and 40-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,15-24 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/29/03; 5/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Response to Restriction/Election requirement and Applicant's Arguments/Remarks, both filed 05/16/07 and the Information Disclosure Statements (IDS), filed 12/29/03 and 05/24/04 is acknowledged.

Applicant's election with traverse of Group I (claims 1-10, 15-24 & 37-39) in the reply filed on 05/16/07 is acknowledged. ((Applicant has also elected species - morphine, however, the Examiner, with regards to the opioid analgesic (claim 2), made no specific election of species requirement. Thus, Applicant's election of species has not been considered or applied)). The traversal is on the ground(s) that "the compositions are similar in nature and while the burden may be slightly higher by examining of all the claims as a single group, the burden would hardly qualify as undue". This is not found persuasive because as stated in the Restriction requirement, the different groups are directed to different products and methods. The different products each entail distinct elements and distinct rates of release or dissolution. The different groups thus have unique issues with regard to patentability, enablement and written description. The different groups would require separate searches in both patent- and non-patent databases and there is no expectation that the searches would be coextensive in scope, thus creating an undue burden upon the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-14, 25-36 and 40-44 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05/16/07.

Claims 1-44 are pending in this action. Claims 11-14, 25-36 and 40-44 have been withdrawn (based on non-elected invention). Claims 1-10, 15-24 and 37-39 are rejected.

Inventorship

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

* * * * *

Claim Objections

Claim 4 is objected to because of the following informalities:

Claim 4 recites "the oral dosage form of any of claims 1-3...". The claim should instead recite, "the oral dosage form of any *one* of claims 1-3..." Appropriate correction is required.

* * * * *

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is indefinite, because the limitations in sections (a) and (b) appear to be duplicates of each other. Clarification is requested.

* * * * *

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10, 15-24 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palermo (WO 99/32120).

Palermo (WO '120) teaches an oral dosage form of an opioid analgesic, comprising an analgesically effective amount of an opioid agonist together with an opioid antagonist, the amount of opioid antagonist including being sufficient to counteract opioid effects if extracted together with the opioid agonist (see p. 6, lines 1-18). The oral dosage forms of the invention are sustained release formulations (p. 8, lines 1-9).

In preferred embodiments, the opioid agonist is hydrocodone, hydromorphone, oxycodone, morphine or pharmaceutically acceptable salts thereof (p. 7, lines 5-6); (p. 13, lines 14-27). Palermo teaches that the dosage forms of the invention may be liquids, tablets, multiparticulates, dispersible powders or granules, hard or soft capsules, lozenges, aqueous or oily suspensions, emulsions, syrups, elixirs, microparticles , buccal tablets, etc. (p. 7, lines 27-31); (p. 8, line 29 – p. 9, line 1). In certain preferred embodiments, the oral dosage forms are sustained release formulations. This may be accomplished via the incorporation of a sustained release carrier into a matrix containing the opioid agonist and opioid antagonist; or via a sustained release coating of a matrix containing the opioid agonist and opioid antagonist, where the sustained release coating contains at least a portion of the sustained release carrier included in the dosage form (p. 8, lines 1-9); (p. 20, lines 16-21).

Palermo teaches that the dosage forms may be coated with one or more materials suitable for the regulation of release or the protection of the formulation. The coatings are provided to permit either pH-dependent or pH-independent release. A pH-dependent coating serves to release the opioid in desired areas of the gastrointestinal tract, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient (p.21, lines 18-29).

Suitable pH-dependent coatings taught include shellac, methacrylic acid ester copolymers, zein and the like (p.22, lines 2-5).

In preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (p. 22, lines 6-14).

Suitable and preferred alkylcellulose polymers taught include ethylcellulose (p. 22, lines 19-25). Acrylic polymers are also disclosed and include acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid) and the like. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties (p. 23, line 10 – p. 24, line 22); (p. 29, lines 7-18).

Plasticizers are also be included in the composition. Suitable plasticizers taught include triethyl citrate, tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin (p. 24, line 24 – p. 25, line 20).

A process for preparing coated beads is disclosed at p. 25, line 21 – p. 28, line 8, wherein it is stated that the controlled release profile of the formulations can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which the plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to the hydrophobic material, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating (p. 26, lines 2-4). Matrix bead formulations are disclosed at page 28. Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials and any pharmaceutically acceptable hydrophobic material or hydrophilic material, which is capable of imparting, controlled release of the active agent and which melts (or softens to the extent necessary to be extruded) may be used in this invention (p. 28, lines 19-30).

Hydrophobic materials disclosed include alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil or mixtures thereof (p. 29, lines 7-9). The hydrophobic material can also be selected from materials such as hydroxyalkylcelluloses, such as hydroxypropylmethyl cellulose (p. 29, lines 9-18). In one embodiment, the ratio of the at least one hydroxyalkylcellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines to a considerable extent, the release rate of the opioid from the formulation (p. 29, line30 – p. 30, line 3).

It is noted that Palermo do not explicitly teach the instant dissolution profiles as claimed by Applicant. However, it is the position of the Examiner that suitable release rates or dissolution profiles can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters

attainable within the art. No unexpected or superior results have been demonstrated, which accrue from the instant dissolution profiles. The Palermo reference explicitly recognizes and teaches oral dosage forms comprising opioid analgesics whereby the dosage forms are effective for the substantial reduction of pain for a twenty-four hour duration period.

Thus, given the teachings of Palermo discussed above, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Claims 1, 4-10, 15-24 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller *et al.* (U.S. Pat. No. 6,326,027).

Miller *et al.* ('027) teach a controlled release preparation for oral administration that contains the opioid analgesic – tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient (see Abstract); (col. 1, lines 1-22). The oral controlled release tramadol preparation is suitable for at least twelve-hourly (e.g., up to twenty-four hourly) administration for the treatment of pain (col. 1, lines 23-25); (col. 7, lines 54-67).

To allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate corresponds to the percent rate of tramadol release, as shown, for instance, in Table 1 (col. 1, lines 40-55). Table 1 demonstrates the following release:

Time (H)	% Released
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

Other preferred tramadol preparations demonstrating in vitro release rates are exemplified in Tables 2-4, shown on columns 1-2.

The controlled release preparation may be presented in the form of granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions and the like (col. 3, lines 32-37).

The active ingredient may be suitably incorporated in a matrix, preferably a controlled release matrix (col. 3, lines 38-46).

Suitable materials for inclusion in a controlled release matrix include hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred (col. 3, line 47 – col. 4, line 13). Additional hydrophobic materials taught include hydrogenated

vegetable oil, hydrogenated castor oil and waxes (col. 5, lines 49-58). Release modifying agents taught include polyethylene glycol (col. 5, lines 59-62).

Other pharmaceutically acceptable ingredients taught that may contribute to controlled release properties include hydroxyalkylcelluloses such as hydroxypropylmethyl cellulose or water insoluble polymers, such as acrylic polymers or copolymers, for example, ethylcellulose (col. 4, lines 36-44); (col. 7, lines 33-37). Water-soluble polymers such as polyvinylpyrrolidone are also disclosed (col. 4, lines 45-55).

The controlled release matrix can also contain surfactants, glidants, e.g., dibutyl sebacate (plasticizer) (col. 4, lines 13-19).

The Examples at columns 8-13 demonstrate various tramadol tablets and preparations of the invention.

While Miller *et al.* do not explicitly teach the instant dissolution profiles as claimed by Applicant, it is the position of the Examiner that suitable release rates or dissolution profiles can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters attainable within the art. No unexpected or superior results have been demonstrated, which accrue from the instant dissolution profiles. The Miller *et al.* patent explicitly teaches controlled release dosage forms comprising an opioid analgesic, which provide analgesia effects for the treatment of pain for a twenty-four hour period or greater. The preparations taught by Miller *et al.* provide for very low release rates of active ingredient, e.g., corresponding to release over a period of greater than 24 hours, such as more than 36 hours.

Thus, given the teachings of Miller *et al.* discussed above, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Claims 1-10, 15-24 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson *et al.* (U.S. Pat. No. 5,952,005).

Olsson *et al.* ('005) teach an oral pharmaceutical preparation containing a therapeutically effective amount of a salt of morphine for once daily administration. The preparation contains particles, which have a core containing a salt of morphine coated with a barrier layer. The barrier layer is formed from a coating liquid that contains at least one water-insoluble barrier forming component from ethyl cellulose, copolymers of acrylic and methacrylic esters and natural or synthetic waxes and a plasticizer. The mean serum concentration of morphine obtained is at least 50% of the maximum serum concentration during at least 12 hours after the administration of a single dose of the preparation (see Abstract); (col. 1, lines 10-21).

The invention provides a multiple unit preparation of morphine consisting of small particles, e.g., crystals, beads or pellets. The multiple unit preparation has a controlled rate of drug release during 15-24 hours for all possible strengths of the preparation (col. 2, lines 45-65). Each coated morphine particle represents and individual controlled release unit, releasing the drug at a predetermined rate. Coated pellets can be used in dosage forms such as capsules and tablets (col. 4, lines 21-27).

Examples of suitable barrier coating materials include ethyl cellulose, Eudragit RS, polyvinyl chloride, natural or synthetic waxes (col. 3, lines 30-40).

Suitable water-soluble components taught include polymers, such as hydroxypropylmethyl cellulose and Eudragit RL (synethesized from acrylic and methacrylic esters) and Eudragit NE (col. 3, lines 41-61).

Plasticizers are also included in the composition (col. 4, lines 5-14). Suitable plasticizers disclosed include triethyl citrate (col. 6, Example 2).

The examples at columns 4-11 demonstrate various morphine preparations of the invention. For instance, Example 2 at column 6 demonstrates a morphine capsule comprising, among other ingredients, morphine hydrochloride, lactose, ethyl cellulose, hydroxypropylmethyl cellulose (HPMC) and triethyl citrate (plasticizer). Release rates of Example 2 are disclosed at column 6, lines 40-45.

The Tables 1-10 further demonstrate various in vitro dissolution rates of morphine hydrochloride.

While Olsson *et al.* do not explicitly teach the instant dissolution profiles as claimed by Applicant, it is the position of the Examiner that suitable release rates or dissolution profiles can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters attainable within the art. No unexpected or superior results have been demonstrated, which accrue from the instant dissolution profiles. The Olsson *et al.* patent explicitly teaches controlled release, multiple unit dosage forms comprising the opioid analgesic, morphine, which provide analgesia effects for the treatment of pain for a twenty-four hour period after administration.

Thus, given the teachings of Olsson *et al.* discussed above, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours. (Wednesdays - Telework).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Humera N. Sheikh

HUMERA N SHEIKH
PRIMARY EXAMINER

Primary Examiner

Art Unit 1615

August 5, 2007

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